Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy for management of cryptogenic stroke

Main editor

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WikiRecs group

A BMJ-Rapid Recommendation on patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy for management of cryptogenic stroke. This is the 10th BMJ-RapidRec, initiated in response to three recently published large trials in the New England Journal of Medicine (Mas 2017;377(11):1011-1021; Saver 2017;377(11):1022-1032; Søndergaard 2017;377:1033-42). Roles: Panel Chair: Fred Spencer Methods Editors: Ton Kuijpers Oversight from RapidRecs executive: Reed Siemieniuk, Thomas Agoritsas, Gordon Guyatt, Per Olav Vandvik Systematic Review Lead: Hassan Mir

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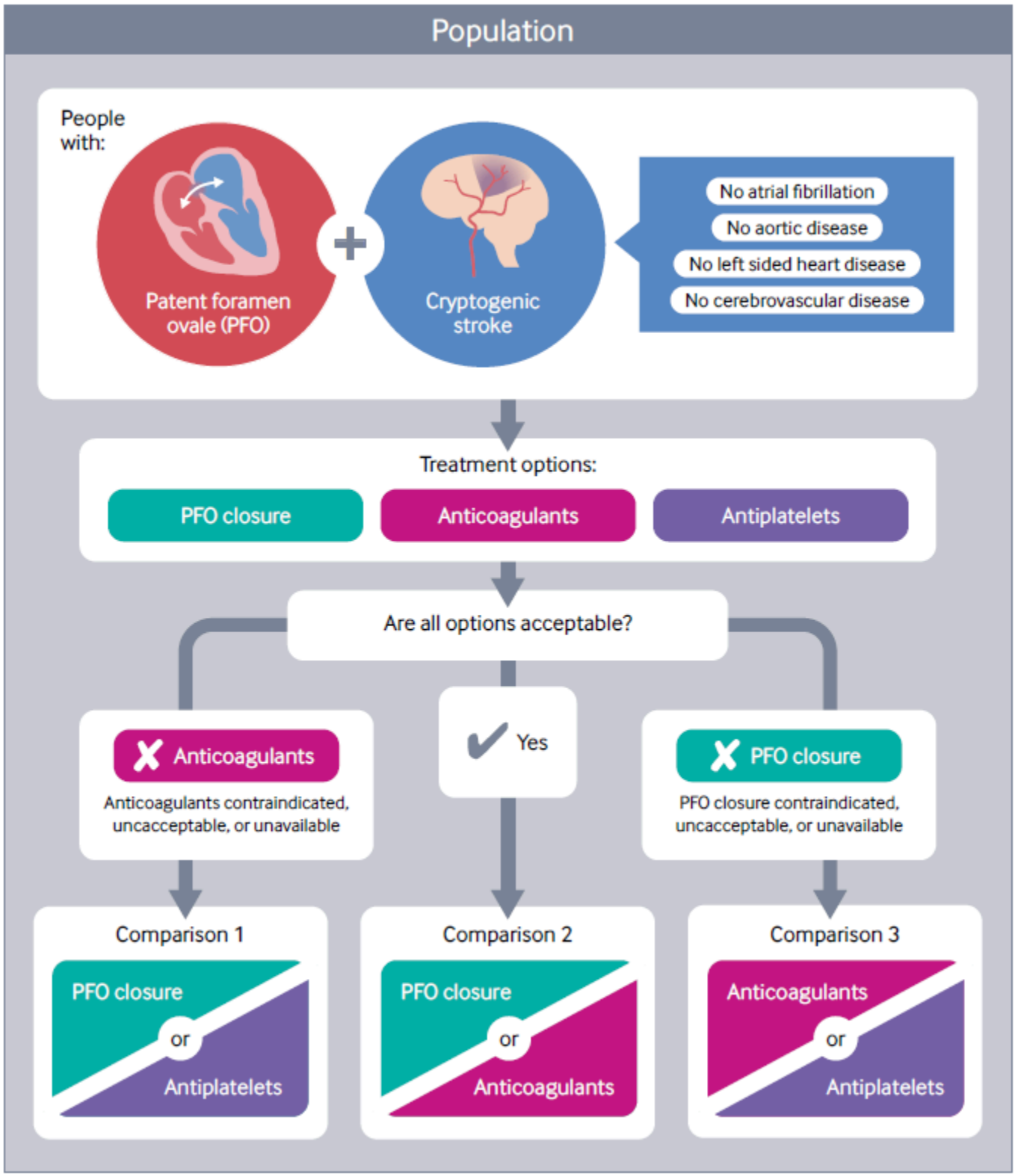
Sponsors/Funding

This guideline was not funded.

Sections

Summary of recommendations

1 - Flow chart of management alternatives for patients with cryptogenic stroke and patent foramen ovale (PFO) (draft picture)



2 - Patients with cryptogenic stroke and patent foramen ovale (PFO)

Strong Recommendation

We recommend PFO closure followed by antiplatelet therapy over antiplatelet therapy alone.

This recommendation is for patients to whom anticoagulants are contraindicated, unacceptable, or unavailable.

Weak Recommendation

We suggest PFO closure followed by antiplatelet therapy over anticoagulation therapy. Discuss both options with each patient.

This recommendation is for patients to whom all options are acceptable.

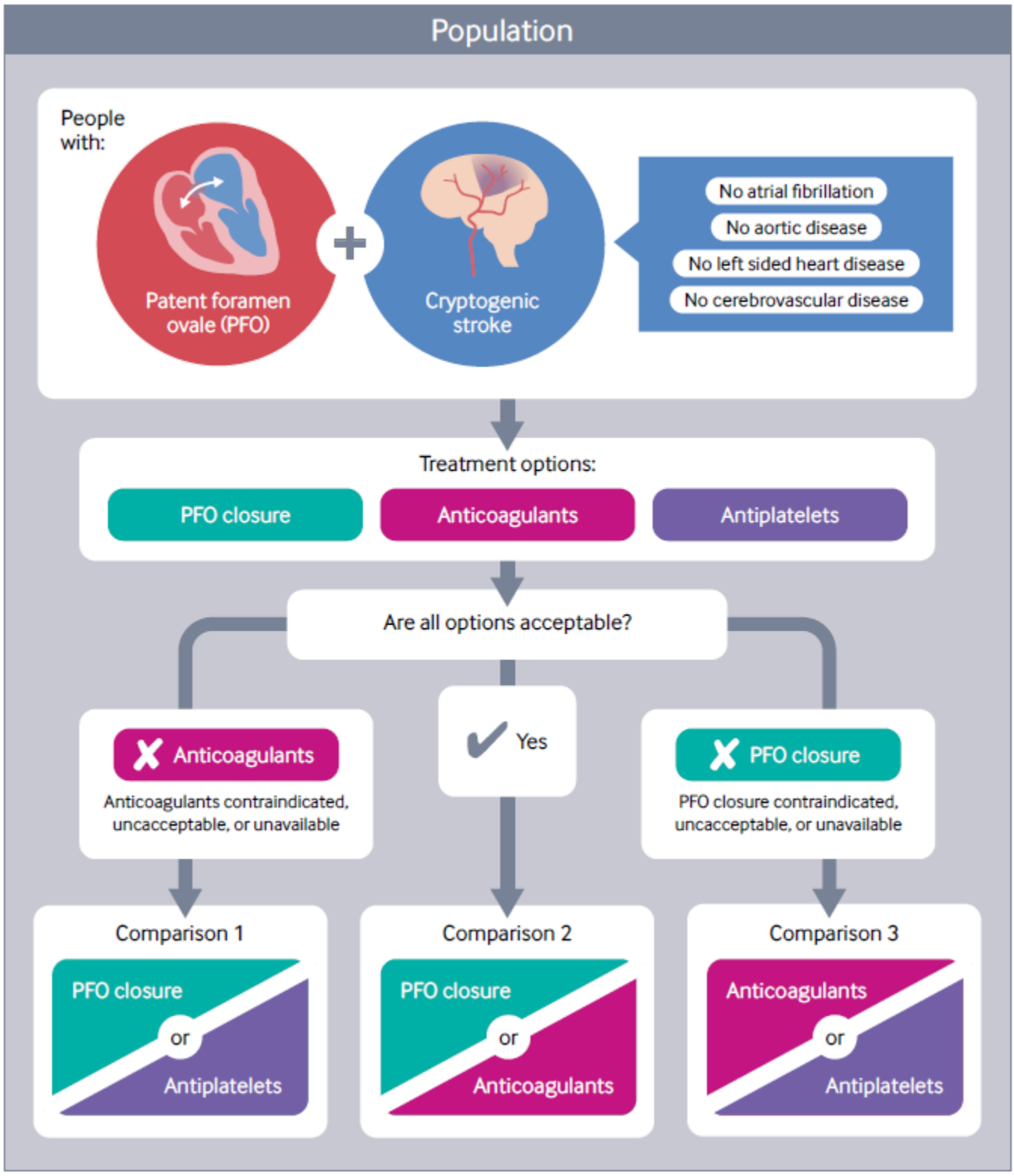
Weak Recommendation

We suggest anticoagulation over antiplatelet therapy. Discuss both options with each patient.

This recommendation is for patients to whom PFO closure is contraindicated, unacceptable, or unavailable.

3 - BMJ Rapid Recommendations Methods and Process

1 - Flow chart of management alternatives for patients with cryptogenic stroke and patent foramen ovale (PFO) (draft picture)



2 - Patients with cryptogenic stroke and patent foramen ovale (PFO)

Strong Recommendation

We recommend PFO closure followed by antiplatelet therapy over antiplatelet therapy alone.

This recommendation is for patients to whom anticoagulants are contraindicated, unacceptable, or unavailable.

Key Info

Benefits and harms

Substantial net benefits of the recommended alternative

The panel agrees that PFO closure followed by antiplatelet therapy versus antiplatelet therapy alone probably has a large decrease in ischemic stroke (8.7% absolute risk reduction over 5 years, moderate quality evidence), carries a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence) and probably has an increase in persistent atrial fibrillation (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation (1.2% absolute risk increase, moderate quality evidence). There probably is little or no difference in death, major bleeding, pulmonary embolism, TIA and systemic embolism (moderate to high quality evidence).

Quality of evidence

Moderate

We had moderate certainty in a decrease in ischemic stroke, high certainty in an increase in device or procedure related adverse events and moderate certainty in an increase in persistent atrial fibrillation. We were moderate certainty that there were little or no difference in death, major bleeding, pulmonary embolism, recurrent TIA and systemic embolism.

Preference and values

No substantial variability expected

Our strong recommendation for PFO closure reflects patients' high value on avoiding an ischemic stroke. The panel, including the patient representatives, felt that that the probable absolute reduction of stroke with PFO closure over 8.7% in 5 years is extremely important. We were concerned about the 3.6% incidence of serious device or procedure related adverse events following PFO closure. However, these events, in contrast to stroke, do not usually result in long term disability, and so, we felt, are much less important.

We were also concerned about the 1,8% absolute increase in incidence of persistent atrial fibrillation following the PFO closure procedure. The main adverse consequence of atrial fibrillation is increased stroke risk, and stroke risk was substantially lower in patients randomized to PFO closure.

Resources and other considerations

No important issues with the recommended alternative

The panel focused on the patient-perspective rather than that of society when formulating the recommendation. Implementation of this recommendation is likely to have an important impact on the costs for health funders which warrants cost-effectiveness data. Over the short term PFO closure is associated with higher costs related to the procedure; however in the long term PFO closure may reduce costs as a result of reduced stroke rates and reduction in the long-term costs of care for stroke patients. *[1]*

Rationale

We issue a strong recommendation for PFO closure followed by antiplatelet therapy because we believe that the probable substantial benefit in stroke reduction, an outcome of very high importance to patients, clearly outweighs the undesirable consequences when compared to antiplatelet therapy alone, in patients to whom anticoagualants are contraindicated or unacceptable.

Clinical Question/ PICO

Population: Patients with cryptogenic stroke
Intervention: PFO closure plus antiplatelet therapy
Comparator: Antiplatelet therapy

Summary

The panel agreed that PFO closure followed by antiplatelet therapy versus antiplatelet therapy alone:

- probably has a large decrease in ischemic stroke (8.7% absolute risk reduction over 5 years, moderate quality evidence)
- carries a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence)
- probably has an increase in persistent atrial fibrillation (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation (1.2% absolute risk increase, moderate quality evidence)
- probably has little or no difference in death, major bleeding, pulmonary embolism, TIA and systemic embolism (moderate to high quality evidence)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Antiplatelet therapy	PFO closure plus antiplatelet therapy	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Ischaemic stroke Standardized to 5 years 8 Critical	Odds Ratio 0.12 (CI 95% 0.04 - 0.27) Based on data from 1,257 patients in 3 studies. (Randomized controlled) Follow up 3.8 years	**100** per 1000	**13** per 1000 Difference: **87 fewer** per 1000 (CI 95% 100 fewer - 33 fewer)	**Moderate** Due to serious imprecision [1]	PFO closure plus antiplatelet therapy probably results in a large decrease in ischemic stroke
Death Standardized to 5 years 9 Critical	Odds Ratio 3.28 (CI 95% 0.2 - 174.22) Based on data from 1,257 patients in 3 studies. (Randomized controlled) Follow up 3.8 years	**3** per 1000	**9** per 1000 Difference: **6 more** per 1000 (CI 95% 3 fewer - 9 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in death
Major bleeding Standardized to 5 years 7 Critical	Odds Ratio 0.48 (CI 95% 0.2 - 1.12) Based on data from 1,257 patients in 3 studies. (Randomized controlled) Follow up 3.8 years	**14** per 1000	**7** per 1000 Difference: **7 fewer** per 1000 (CI 95% 14 fewer - 1 more)	**Moderate** Due to serious imprecision [3]	There is probably little or no difference in major bleeding
Persistent atrial fibrillation or Flutter Standardized to 1 year	Relative risk 4.84 (CI 95% 1.91 - 12.26) Based on data from 3,560 patients in 6 studies. (Randomized controlled)	**5** per 1000	**23** per 1000 Difference: **18 more** per 1000 (CI 95% 5 more - 56 more)	**Moderate** Due to serious risk of bias [4]	PFO closure plus antiplatelet therapy probably increases persistent atrial fibrillation

6 Important	Follow up 3.9 years				
Transient atrial fibrillation or flutter Standardized to 1 year 6 Important	Relative risk 3.76 (CI 95% 1.74 - 8.1) Based on data from 3,560 patients in 6 studies. (Randomized controlled) Follow up 3.9 years	**5** per 1000	**17** per 1000 Difference: **12 more** per 1000 (CI 95% 3 more - 31 more)	**Moderate** Due to serious risk of bias [5]	PFO closure plus antiplatelet therapy probably increases transient atrial fibrillation
Device or procedure related adverse events Standardized to 1 year 6 Important	Based on data from 3,560 patients in 6 studies. (Randomized controlled) Follow up 3.9 years	**0** per 1000	**36** per 1000 Difference: **36 more** per 1000 (CI 95% 23 more - 50 more)	**High** 6	PFO closure plus antiplatelet therapy increase device or procedure related adverse events
Pulmonary embolism Standardized to 5 years 6 Important	Odds Ratio 1.01 (CI 95% 0.09 - 11.21) Based on data from 1,137 patients in 2 studies. (Randomized controlled) Follow up 4.3 years	**5** per 1000	**5** per 1000 Difference: **0 fewer** per 1000 (CI 95% 5 fewer - 48 more)	**High**	PFO plus antiplatelet therapy has no effect on pulmonary embolism
Transient ischaemic attack Standardized to 5 years 6 Important	Odds Ratio 0.82 (CI 95% 0.32 - 2.11) Based on data from 1,257 patients in 3 studies. (Randomized controlled) Follow up 3.8 years	**34** per 1000	**28** per 1000 Difference: **6 fewer** per 1000 (CI 95% 34 fewer - 15 more)	**Moderate** Due to serious imprecision [7]	There is probably little or no difference in transient ischaemic attack
Systemic embolism Standardized to 5 years	Odds Ratio 0.83 (CI 95% 0.13 - 7.25) Based on data from 1,257 patients in 3 studies. (Randomized controlled) Follow up 3.8 years	**6** per 1000	**5** per 1000 Difference: **1 fewer** per 1000 (CI 95% 6 fewer - 4 more)	**High**	There is little or no difference in systemic embolism
Total Afib (test)	Relative risk 4.5 (CI 95% 2.35 - 8.6) Based on data from 3,560	**11**	**50**		

	patients in 6 studies. (Randomized controlled) Follow up 3.9	per 1000 per 1000 Difference: **39 more** per 1000 (CI 95% 15 more - 84 more)	

Practical issues	Antiplatelet therapy	PFO closure plus antiplatelet therapy	Both
 Medication routine	1 dose per day		1 dose per day
 Tests and visits		May include 1 or 2 visits to the cardiologist in the first 6 months followed by an appointment every 1-2 years.	
 Procedure and device		The PFO device will be implanted using a catheter (long, thin, flexible, hollow tube), inserted through a small cut made at the inner thigh (groin), with local anasthesia and moderate sedation or under general anaesthesia. The procedure takes under 2 hours. In-hospital stay is usually one day.	
 Recovery and adaptation		Most activities can be resumed within a few days, with full recovery within a few weeks.	
 Costs and access	Most can take a low-cost medication available without a prescription.		Most can take a low-cost medication available without a prescription.
 Exercise and activities		Need to avoid strenuous activity during recovery.	

Work and education

Time to return to work depends on speed of recovery.

Travel and driving

Driving may be limited during recovery.

1. **Risk of bias: No serious .** Despite of inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, we decided not to downgrade since we rated ischemic stroke as an objective outcome (borderline decision). ; **Inconsistency: No serious .** Borderline decision I2 54%, not rated down. ; **Indirectness: No serious . Imprecision: Serious .** Low number of events. ; **Publication bias: No serious .**
2. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence intervals, included appreciable harm. Low number of events. ; **Publication bias: No serious .**
3. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of events ; **Publication bias: No serious .**
4. **Risk of bias: Serious .** Not clearly stated how this was measured or assessesd with prolonged ECG monitoring. Also, it is not clear for all events whether it was transient or persistent. ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: No serious . Publication bias: No serious .**
5. **Risk of bias: Serious .** Not clearly stated how this was measured or assessesd with prolonged ECG monitoring. Also, it is not clear for all events whether it was transient or persistent. ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: No serious . Publication bias: No serious .**
6. **Inconsistency: No serious .** Inconsistency 1 study as high 60/100 and 1 as low as 10/1000., Point estimates vary widely. Not rated down. ; **Indirectness: No serious . Publication bias: No serious .**
7. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence intervals, included both appreciable benefit and harm. Low number of events. ; **Publication bias: No serious .**

Weak Recommendation

We suggest PFO closure followed by antiplatelet therapy over anticoagulation therapy. Discuss both options with each patient.

This recommendation is for patients to whom all options are acceptable.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

The panel agreed that PFO closure followed by antiplatelet therapy versus anticoagulation may have little or no difference in ischaemic stroke (1.6% absolute risk reduction over 5 years, low quality evidence), probably decreases major bleeding (2.0% absolute risk reduction over 5 years, moderate quality evidence), has a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence) and probably has an increase in persistent atrial fibrillation (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation (1.2% absolute risk increase, moderate quality evidence). There probably is little or no

difference in death, pulmonary embolism, TIA and systemic embolism (moderate quality evidence).

Quality of evidence Low

There is low certainty that there is little or no difference in ischemic stroke, moderate certainty for a decrease in major bleeding and an increase in persistent atrial fibrillation. There is high certainty in a risk of device or procedure related adverse events. There is moderate certainty that there is little or no difference in death, recurrent TIA, systemic embolism, pulmonary embolism.

Preference and values Substantial variability is expected or uncertain

The weak recommendation for PFO closure versus anticoagulation reflects - in addition to the low certainty in the estimates of effect - that most panel members felt that whereas most serious complications of PFO closure are usually short-term, anticoagulation imposes a lifelong increased risk of major bleeding. The panel felt that the majority of fully informed patients would accept the mostly transient risk of major adverse events rather than the long-term bleeding risk, but that a substantial minority would choose anticoagulation.

Resources and other considerations No important issues with the recommended alternative

The panel focused on the patient-perspective rather than that of society when formulating the recommendation. Implementation of this recommendation is likely to have an important impact on the costs for health funders which warrants cost-effectiveness data. Over the short term PFO closure is associated with higher costs related to the procedure; however in the long term PFO closure may reduce costs as a result of reduced stroke rates and reduction in the long-term costs of care for stroke patients. *[1]*

Rationale

We issue a weak recommendation for PFO closure versus anticoagulation because of the large uncertainty and possibly little or no difference in ischemic stroke between PFO closure and anticoagulation. In addition to the low certainty in the estimates of effect - that most panel members felt that whereas most serious complications of PFO closure are usually short-term, anticoagulation imposes a lifelong increased risk of major bleeding. The panel felt that the majority of fully informed patients would accept the mostly transient risk of major adverse events rather than the long-term bleeding risk, but that a substantial minority would choose anticoagulation.

Clinical Question/ PICO

Population: Patients with cryptogenic stroke
Intervention: PFO closure plus antiplatelet therapy
Comparator: Anticoagulation

Summary

The panel agreed that PFO closure followed by antiplatelet therapy versus anticoagulation:

- may result in little or no difference in ischaemic stroke (1.6% absolute risk reduction over 5 years, low quality evidence)
- probably decreases major bleeding (2.0% absolute risk reduction over 5 years, moderate quality evidence)
- has a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence)
- probably has an increase in persistent atrial fibrillation (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation (1.2% absolute risk increase, moderate quality evidence)
- probably has little or no difference in death, pulmonary embolism, TIA and systemic embolism (moderate quality evidence)

Outcome Timeframe	Study results and measurements	Absolute effect estimates Anticoagulation	 PFO closure plus antiplatelet therapy	Certainty in effect estimates (Quality of evidence)	Plain text summary
Ischaemic stroke Standardized to 5 years 8 Critical	Odds Ratio 0.44 (CI 95% 0.08 - 3.83) Based on data from 353 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**29** per 1000	**13** per 1000 Difference: **16 fewer** per 1000 (CI 95% 29 fewer - 10 more)	**Low** Due to very serious imprecision [1]	There may be little or no difference in ischaemic stroke
Ischaemic stroke (modelling data from VTE literature) Standardized to 5 years 8 Critical	Odds Ratio 0.93 (CI 95% 0.31 - 2.76) (Randomized controlled)	**29** per 1000	**27** per 1000 Difference: **2 fewer** per 1000 (CI 95% 20 fewer - 47 more)	**Low** Due to serious imprecision and serious indirectness [2]	There may be little or no difference in ischaemic stroke
Death Standardized to 5 years 9 Critical	Relative risk 0.69 (CI 95% 0.02 - 32.36) Based on data from 353 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**13** per 1000	**9** per 1000 Difference: **4 fewer** per 1000 (CI 95% 13 fewer - 9 more)	**Moderate** Due to serious imprecision [3]	There is probably little or no difference in death
Major bleeding Standardized to 5 years 7 Critical	Odds Ratio 0.26 (CI 95% 0.07 - 0.82) Based on data from 353 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**27** per 1000	**7** per 1000 Difference: **20 fewer** per 1000 (CI 95% 27 fewer - 2 fewer)	**Moderate** Due to serious imprecision [4]	PFO closure plus antiplatelet therapy probably decreases major bleeding
Major bleeding (modelling data from VTE literature) Standardized to 5 years 7 Critical	Odds Ratio 0.28 (CI 95% 0.13 - 0.55) (Randomized controlled)	**24** per 1000	**7** per 1000 Difference: **17 fewer** per 1000 (CI 95% 21 fewer - 11 fewer)	**Moderate** Due to serious indirectness [5]	PFO closure plus antiplatelet therapy probably decreases major bleeding
Persistent atrial fibrillation or flutter	Relative risk 4.84 (CI 95% 1.91 - 12.26) Based on data from 3,560	**5** per 1000	**23** per 1000	**Moderate** Due to serious risk of bias [6]	PFO closure plus antiplatelet therapy probably increases

Standardized to 1 year 6 Important	patients in 6 studies. (Randomized controlled) Follow up 3.9 years	Difference: **18 more** per 1000 (CI 95% 5 more - 56 more)		persistent atrial fibrillation
Transient atrial fibrillation or flutter Standardized to 1 year 6 Important	Relative risk 3.76 (CI 95% 1.74 - 8.1) Based on data from 3,560 patients in 6 studies. (Randomized controlled) Follow up 3.9 years	**5** per 1000 **17** per 1000 Difference: **12 more** per 1000 (CI 95% 3 more - 31 more)	**Moderate** Due to serious risk of bias [7]	PFO closure plus antiplatelet therapy probably increases transient atrial fibrillation
Device or procedure related adverse event Standardized to 1 year 6 Important	Based on data from 3,560 patients in 6 studies. (Randomized controlled) Follow up 3.9 years	**0** per 1000 **36** per 1000 Difference: **36 more** per 1000 (CI 95% 23 more - 50 more)	**High**	PFO closure plus antiplatelet therapy increases device or procedure related adverse events
Transient ischaemic attack Standardized to 5 years 6 Important	Odds Ratio 1.27 (CI 95% 0.4 - 4.52) Based on data from 353 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**22** per 1000 **28** per 1000 Difference: **6 more** per 1000 (CI 95% 22 fewer - 22 more)	**Moderate** Due to serious imprecision [8]	There is probably little or no difference in transient ischaemic attack
Pulmonary embolism (modelling data from VTE literature) Standardized to 5 years 6 Important	Odds Ratio 9.09 (CI 95% 3.7 - 25) (Randomized controlled)	**1** per 1000 **5** per 1000 Difference: **4 more** per 1000 (CI 95% 1 more - 13 more)	**Moderate** Due to serious indirectness [9]	There is probably little or no difference in pulmonary embolism
Systemic embolism Standardized to 5 years	Odds Ratio 291 (CI 95% 0 - 999) Based on data from 353 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**0** per 1000 **0** per 1000 Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)	**Moderate** Due to serious imprecision [10]	There is probably little or no difference in systemic embolism

Practical issues	Anticoagulation	PFO closure plus antiplatelet therapy	Both
 Medication routine	One or two doses per day.		
 Tests and visits	Initial frequent testing required to achieve appropriate dose. Periodic testing required while taking medication.	May include 1 or 2 visits to the cardiologist in the first 6 months followed by an appointment every 1-2 years.	
 Procedure and device		The PFO device will be implanted using a catheter (long, thin, flexible, hollow tube), inserted through a small cut made at the inner thigh (groin), with local anasthesia and moderate sedation or under general anaesthesia. The procedure takes under 2 hours. In-hospital stay is usually one day.	
 Recovery and adaptation		Most activities can be resumed within a few days, with full recovery within a few weeks.	
 Adverse effects, interactions and antidote	Certain medicines may increase one's risk of bleeding, and some may increase the risk of stroke, by reducing the effect of the anticoagulan.		
 Pregnancy and nursing	Women who are pregnant or considering pregnancy may need to change their medication, and may face considerable complications of pregnancy and birth being on anticoagulation or heparine during pregnancy.		

	Costs and access	Newer medications cost more, but require less monitoring.	
	Food and drinks	Dietary restrictions may apply.	
	Exercise and activities	May need to limit activities with high injury risk.	Need to avoid strenuous activity during recovery.
	Work and education		Time to return to work depends on speed of recovery.
	Travel and driving		Driving may be limited during recovery.

1. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Very Serious .** Wide confidence interval. Low number of events. ; **Publication bias: No serious .**
2. **Inconsistency: No serious . Indirectness: Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism. ; **Imprecision: Serious .** Wide confidence intervals, includes both appreciable benefit and harm. ; **Publication bias: No serious .**
3. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence intervals, includes both appreciable benefit and harm. Low number of events. ; **Publication bias: No serious .**
4. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence interval, included a not important benefit. Low number of events. ; **Publication bias: No serious .**
5. **Inconsistency: No serious . Indirectness: Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism. ; **Imprecision: No serious . Publication bias: No serious .**
6. **Risk of bias: Serious .** Not clearly stated how this was measured or assessesd with prolonged ECG monitoring. Also, it is not clear for all events whether it was transient or persistent. ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: No serious . Publication bias: No serious .**
7. **Risk of bias: Serious .** Not clearly stated how this was measured or assessesd with prolonged ECG monitoring. Also, it is not clear

for all events whether it was transient or persistent ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: No serious . Publication bias: No serious .**

8. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence interval, includes both appreciable benefit and harm. Low number of events. ; **Publication bias: No serious .**
9. **Inconsistency: No serious . Indirectness: Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism ; **Imprecision: No serious .** Low number of patients (not rated down for imprecision). ; **Publication bias: No serious .**
10. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of events. ; **Publication bias: No serious .**

Weak Recommendation

We suggest anticoagulation over antiplatelet therapy. Discuss both options with each patient.

This recommendation is for patients to whom PFO closure is contraindicated, unacceptable, or unavailable.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

The panel agreed that anticoagulation versus antiplatelet therapy may decrease ischaemic stroke (7.1% absolute risk reduction over 5 years, low quality evidence), probably increases major bleeding (1.2% absolute risk increase over 5 years, moderate quality evidence) and probably has little or no difference in death, pulmonary embolism, TIA and systemic embolism (moderate quality evidence).

Quality of evidence

Low

There is low certainty that there was a decrease in ischemic stroke, moderate certainty for an increase in major bleeding. There is moderate certainty that there is little or no difference in death, pulmonary embolism, TIA and systemic embolism.

Preference and values

Substantial variability is expected or uncertain

A typical patient places a high value in a possible absolute reduction of stroke with anticoagulation of 7.1% in 5 years and would therefore value the possible benefit in stroke reduction higher than the probable increased risk of major bleeding. A systematic review *[2]* and a primary study *[3]* regarding values and preferences on thromboprophylaxis treatment of patients with atrial fibrillation were highly variable, however both strongly suggest that patients value preventing strokes considerably more than they are concerned with increased risk of bleeding. However, there is substantial uncertainty in our estimates for stroke reduction – how this uncertainty would influence decisions is likely to vary substantially. Therefore we issue a weak recommendation for anticoagulation. Both options need to be discussed with the patients, ideally in a process of shared decision making.

Resources and other considerations

No important issues with the recommended alternative

The panel focused on the patient-perspective rather than that of society when formulating the recommendation. Implementation of this recommendation is likely to have an important impact on the costs for health funders which warrants cost-effectiveness data.

Rationale

The main reason why we make a weak recommendation for anticoagulation versus antiplatelet therapy is we are uncertain about the

benefit of anticoagulation on ischemic stroke, an outcome we feel a typical patient places a high value on. Another reason that drove this weak recommendation is anticoagulation probably increases major bleeding. Therefore we feel the possible benefit less clearly outweighs the undesirable consequences of antigoagulation versus antiplatelet therapy.

Clinical Question/ PICO

Population: Patients with cryptogenic stroke
Intervention: Anticoagulation
Comparator: Antiplatelet

Summary

The panel agreed that anticoagulation versus antiplatelet therapy:

- may decrease ischaemic stroke (7.1% absolute risk reduction over 5 years, low quality evidence)
- probably increases major bleeding (1.2% absolute risk increase over 5 years, moderate quality evidence)
- probably has little or no difference in death, pulmonary embolism, TIA and systemic embolism (moderate quality evidence)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Antiplatelet	Anticoagulation	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Ischaemic stroke Standardized to 5 years 8 Critical	Odds Ratio 0.27 (CI 95% 0.03 - 1.21) Based on data from 361 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**100** per 1000	**29** per 1000 Difference: **71 fewer** per 1000 (CI 95% 100 fewer - 17 more)	**Low** Due to very serious imprecision [1]	Anticoagulation may decrease ischaemic stroke
Ischaemic stroke (modelling data from VTE literature) Standardized to 5 years 8 Critical	Odds Ratio 0.17 (CI 95% 0.08 - 0.36) (Randomized controlled)	**100** per 1000	**19** per 1000 Difference: **81 fewer** per 1000 (CI 95% 91 fewer - 62 fewer)	**Low** Due to very serious indirectness [2]	Anticoagulation may decrease ischaemic stroke
Death Standardized to 5 years 9 Critical	Odds Ratio 4.81 (CI 95% 0.31 - 224.43) Based on data from 408 patients in 2 studies. (Randomized controlled) Follow up 3.2 years	**3** per 1000	**13** per 1000 Difference: **10 more** per 1000 (CI 95% 3 fewer - 357 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in death

Major Bleeding Standardized to 5 years 7 Critical	Odds Ratio 1.9 (CI 95% 0.68 - 5.53) Based on data from 408 patients in 2 studies. (Randomized controlled) Follow up 3.2 years	**14** per 1000	**26** per 1000 Difference: **12 more** per 1000 (CI 95% 5 fewer - 65 more)	**Moderate** Due to serious imprecision [4]	Anticoagulation probably increases major bleeding
Major bleeding (modelling data from VTE literature) Standardized to 5 years 7 Critical	Odds Ratio 1.77 (CI 95% 1.36 - 2.31) (Randomized controlled)	**14** per 1000	**25** per 1000 Difference: **11 more** per 1000 (CI 95% 5 more - 18 more)	**Moderate** Due to serious indirectness [5]	Anticoagulation probably increases major bleeding
Transient ischaemic attack Standardized to 5 years 6 Important	Odds Ratio 0.65 (CI 95% 0.19 - 1.98) Based on data from 361 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**34** per 1000	**22** per 1000 Difference: **12 fewer** per 1000 (CI 95% 34 fewer - 24 more)	**Low** Due to very serious imprecision [6]	There may be little or no difference in transient ischaemic attack
Pulmonary embolism (modelling data from VTE literature) Standardized to 5 years 6 Important	Odds Ratio 0.11 (CI 95% 0.04 - 0.37) (Randomized controlled)	**5** per 1000	**1** per 1000 Difference: **4 fewer** per 1000 (CI 95% 5 fewer - 3 fewer)	**Moderate** Due to serious indirectness [7]	There is probably little or no difference in pulmonary embolism.
Systemic embolism Standardized to 5 years	Based on data from 361 patients in 1 studies. (Randomized controlled) Follow up 5.3 years	**0** per 1000	**0** per 1000 Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)	**Moderate** Due to serious imprecision [8]	There is probably little or no difference in systemic embolism

Practical issues	Antiplatelet	Anticoagulation	Both

 Medication routine	1 dose per day.	One or two doses per day.
 Tests and visits		Initial frequent testing required to achieve appropriate dose. Periodic testing required while taking medication.
 Adverse effects, interactions and antidote		Certain medicines may increase one's risk of bleeding, and some may increase the risk of stroke, by reducing the effect of the anticoagulan.
 Pregnancy and nursing		Women who are pregnant or considering pregnancy may need to change their medication, and may face considerable complications of pregnancy and birth being on anticoagulation or heparine during pregnancy.
 Costs and access	Most can take a low-cost medication available without a prescription.	Newer medications cost more, but require less monitoring.
 Food and drinks		Dietary restrictions may apply.
 Exercise and activities		May need to limit activities with high injury risk.

1. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Very Serious .** Wide confidence interval, includes appreciable harm. Low number of events. ; **Publication bias: No serious .**
2. **Inconsistency: No serious . Indirectness: Very Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism ; **Imprecision: No serious**

. Publication bias: No serious .

3. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Very Serious .** Wide confidence interval, includes both appreciable benefit and harm. Low number of events. ; **Publication bias: No serious .**
4. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Wide confidence intervals, Low number of events. ; **Publication bias: No serious .**
5. **Inconsistency: No serious . Indirectness: Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism. We did not rate down with two levels because we feeld the outocme is less indorect compared to VTE literature than Ischaemic stroke. ; **Imprecision: No serious . Publication bias: No serious .**
6. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Very Serious .** Wide confidence interval, includes both appreciable harm and benefit. Low number of events. ; **Publication bias: No serious .**
7. **Inconsistency: No serious . Indirectness: Serious .** In addition to the direct evidence from randomized trials in patients with PFO and a cryptogenic ischaemic stroke, we additionally considered external evidence from randomized trials that assessed the impact of anticoagulation vs. antiplatelet therapy for the secondary prevention of venous thromboembolism. ; **Imprecision: No serious . Publication bias: No serious .**
8. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of events. ; **Publication bias: No serious .**

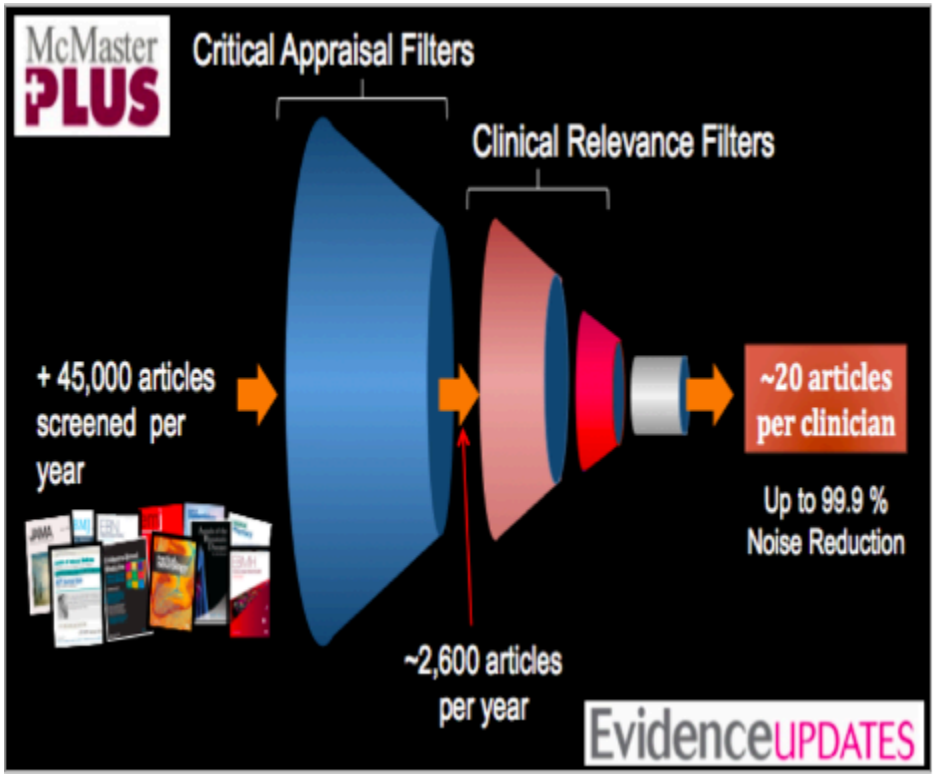
3 - BMJ Rapid Recommendations Methods and Process

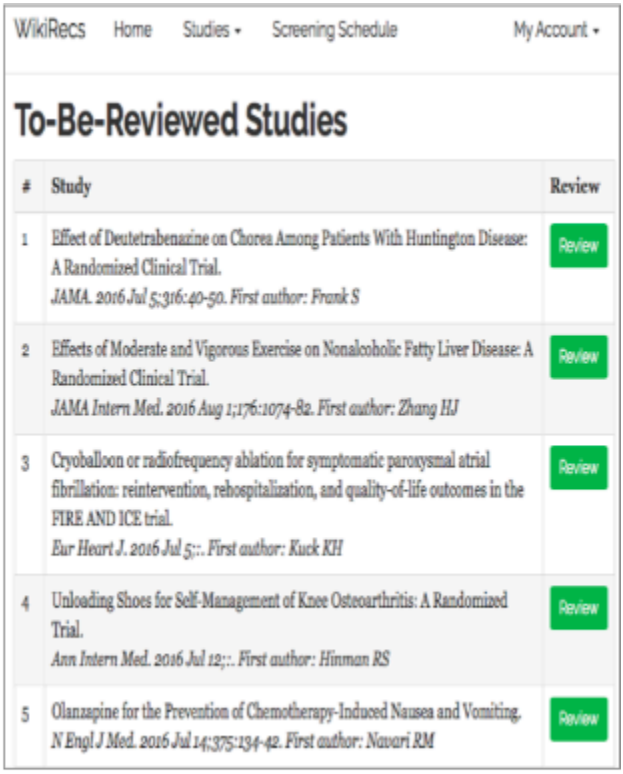
About BMJ Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:
    - Formal monitoring through McMaster Premium LiteratUre Service (PLUS)
    - Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients





2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.
3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:
    - A rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients
    - Parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.
    - The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]
    - Further research may be conducted including:

- A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the clinical question, a key component when calculating the estimates of absolute effects of the intervention.
- A systematic review on the preferences and values of patients on the topic.

4. Disseminate the rapid recommendations through:
   - Publication of the research in *BMJ* journals
   - Short summary of recommendations for clinicians published in *The BMJ*
   - Press release and/or marketing to media outlets and relevant parties such as patient groups
   - Links to *BMJ* group's *Best Practice* point of care resource
   - MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves:
1. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]
2. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user-friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process. The following panel members are important:
- At least one author of the individual systematic reviews.
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development.

Any potential conflicts of interest are managed with extreme prudence:
- No panel member can have a financial interest – as assessed by the panel chair, the *RapidRecs* executive team or *The BMJ* editors as relevant to the topic.
- No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ *Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, the panel recruitment of content experts and community panel members was challenging. Content experts in this area are infectious diseases experts, many of whom have financial conflicts of interests through interactions with the pharmaceutical industry through advisory boards and participation in industry-funded trials. The group reached out to more than 17 potential panel members who were eventually excluded from participating because of conflicts – notably, all of these persons had not disclosed any relevant conflicts on related and recent publications in the topic area. Many more potential panel members were not recruited because of publicly declared conflicts. The chair and MAGIC team were able, with considerable effort and ingenuity, to recruit several excellent and unconflicted content experts.*

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:
1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)
Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to The BMJ. Additional teleconferences are arranged as needed.

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, two large-group teleconferences were arranged. First, content experts provided crucial input to evidence assessment (e.g. subgroups to identify). For the recommendation formulation phase the panel needed two teleconferences to discuss all elements in detail, followed by more than 100 e-mails with specific issues to be sorted out. Multiple teleconferences were held to allow the scheduling flexibility required so that all could participate.

How we move from research findings to recommendations

What information is considered?
The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the BMJ Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?
The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible."***
• This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content i available. • We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",**
• Interests of each panel member are declared prior to involvement and published with the rapid recommendations. • No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*. • No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issu for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic. • The Chair must have methods expertise, a clinical background and no financial or intellectual interests. • Funders and pharmaceutical companies have no role in these recommendations.
3. Guideline Development Group Composition **"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG."**

- The RapidRecs group will aim to include representation from most or every major geographic region in the world, with specific efforts made achieve gender-balance.
- We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available.
- Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.

4. Clinical Practice Guideline–Systematic Review Intersection
"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes."

- Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton.
- The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication an continuity in the process.

5. Establishing Evidence Foundations for and Rating Strength of Recommendations
"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations."

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
  - Quality of the evidence[7]
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)

- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.[8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus proce customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations
"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated."

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and with an individual patient.

7. External review
"External reviewers should comprise a full spectrum of relevant stakeholders....., authorship should be kept confidential....., all reviewer comment

should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available t general public for comment..."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy.
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *RapidRecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable.
- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period o six months after publication.

8. Updating
"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence."

- The *RapidRecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

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